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(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: 85106522.7

(51) Int. Cl.<sup>4</sup>: **C 07 J 71/00**

(22) Date of filing: 28.05.85

(30) Priority: 11.06.84 IT 2134384

(43) Date of publication of application:  
18.12.85 Bulletin 85/51

(84) Designated Contracting States:  
AT BE CH DE FR GB IT LI LU NL SE

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(54) **A process for the preparation of 16,17 acetals of pregnane derivatives and compounds obtained therefrom.**

(57) **A process for the preparation of 16,17 acetals of pregnane derivatives by trans-ketalization of 16,17-acetonides is described.**

In the instance of the preparation of 16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ ,21-dihydroxypregna-1,4-diene-3,20-dione, a compound having useful therapeutic properties, known also as budesonide, it is possible to obtain the more active epimer with high selectivity and remarkable economic advantages in comparison with the known methods.

New 16,17 acetals of pregnane derivatives, which can be prepared by the method of the invention, are also described.

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"A process for the preparation of 16,17 acetals of pregnane derivatives and compounds obtained therefrom"

The present invention concerns a process for the preparation of 16,17 acetals of pregnane derivatives starting from the corresponding 16,17-acetonides.

5 More particularly, the process of the invention is conveniently applicable to the synthesis of 16 $\alpha$ ,17 $\alpha$ -butylidendioxy-11 $\beta$ ,21-dihydroxypregna-1,4-diene-3,20-dione, described in US Patent No. 3,929,768 and GB Patent No. 1,429,922, a useful compound in  
10 human therapy, known also as budesonide, and to the synthesis of similar compounds.

Analogous compounds, which can be obtained by the process of the invention, are described also in the European patent application No. 0 054 010 of June  
15 16th, 1982.

The invention refers moreover to new 16,17 acetals of pregnane derivatives, obtained according to said process.

The known methods for the preparation of said  
20 pregnene or pregnadiene 16,17 acetals are based upon the reaction of 16 $\alpha$ ,17 $\alpha$  diols with aldehydes (butyraldehyde in the instance of budesonide) in the presence of acids and suffer therefore from the drawbacks connected with the use of 16 $\alpha$ ,17 $\alpha$  diols, as starting  
25 materials, which are compounds difficult to prepare and purify and unstable because they tend to

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isomerize to D-homo-steroids. The known methods, moreover, do not exhibit any selectivity since the two epimers are obtained in almost equal amounts.

Moreover, said acetals exist as couples of 5 epimers which can be separated with difficulty by means of cumbersome techniques which are difficult to be applied industrially, such as column chromatography, HPLC (high performance liquid chromatography) or gel-filtration as described in GB Patent No. 10 1,428,416 and US Patent No. 3,928,326. Further, in the specific case of budesonide, one of the two epimers (hereinafter designated as "B") proved to be more active than the other one.

It is therefore evident the importance of an 15 industrially applicable preparation method, which allows to obtain the preferred isomer with high selectivity and remarkably lower costs than that of the isomers mixture obtained according to the known process.

20 The process according to the present invention allows to overcome the drawbacks of the prior art and consists in a direct transketalization reaction with aldehydes on 16,17-acetonides, in the presence of hydrohalogen acids.

25 It is known that steroidal acetals or cyclic ketals can be hydrolized to diol compounds by treatment with aqueous HF or HCl, at temperatures ranging from -30° to +25°C (US Reissue No. 26877, 12-5-1970).

In the published German patent application No. 30 2,448,548 the preparation of 16,17 acetals or ketals

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starting from 9,11-epoxy-16,17-diols with aldehydes or ketones in the presence of hydrogen halides is described.

Quite surprisingly, with respect to the above 5 cited documents and to what is known in the art, the method of the invention occurs in almost quantitative yields and, even more surprisingly, the more active epimer is almost exclusively obtained.

The steric selectivity can also be suitably 10 controlled by changing the reaction conditions. Particularly, by changing the reaction temperature, it is possible to obtain products containing from 50% to more than 90% of the more active epimer (B epimer).

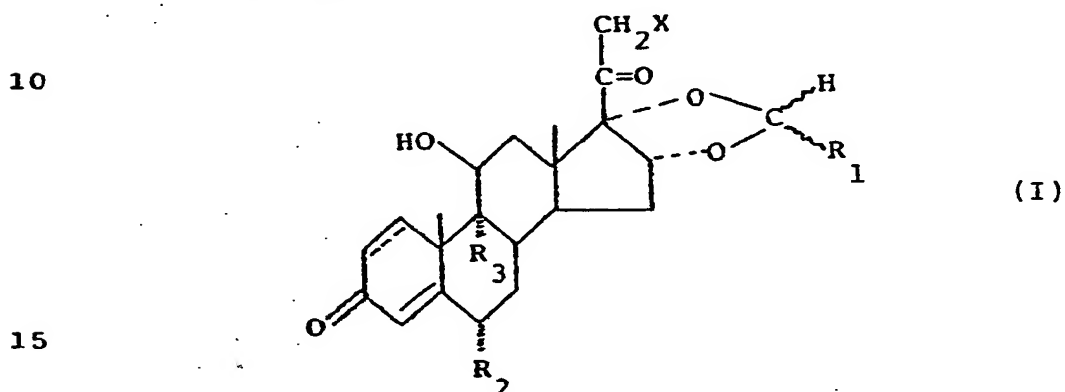
Another aspect of the present invention is the 15 transformation of the less active epimer of a 16,17-acetal of pregnane derivatives into the more active epimer.

A further essential feature of the invention resides in the use, as starting materials, of 16,17- 20 ketals, preferably 16,17-acetonides, which, differently from the 16,17-diol compounds up to now considered as the sole precursors for the preparation of the corresponding acetals, are stable, easily available compounds which can be easily purified. The acetonides, 25 for the above cited reasons, are often used for the purification of diols and can be therefore considered to be precursors of the latter, and not vice versa, having moreover a lower production cost.

As a consequence, the process of the invention 30 is particularly convenient, also leaving the excep-

tionally high yields obtained out of consideration,  
and it is possible to prepare new compounds previously impossible to be prepared because of the unavailability or the instability of the corresponding diols.

The compounds which can be prepared by the process object of the invention have the following general formula:



wherein  $R_1$  represents a  $C_1-C_{12}$  alkyl group;

X may be OH, Cl, F or  $-OCOR$  groups wherein R represents a  $C_1-C_{12}$  alkyl group;

20  $R_2$  may be hydrogen, fluorine or methyl;

$R_3$  may be hydrogen, fluorine or chlorine.

Many of the compounds of formula I are new and are comprised in the scope of the invention.

Particularly, new compounds according to the invention are:

6-fluoro-16 $\alpha$ ,17 $\alpha$ -butyridenedioxy-11 $\beta$ ,21-dihydroxypregna-1,4-diene-3,20-dione;

9-fluoro-21-chloro-16 $\alpha$ ,17 $\alpha$ -butyridenedioxy-11 $\beta$ -hydroxypregna-4-ene-3,20-dione;

9-chloro-16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ ,21-dihydroxypregna-1,4-diene-3,20-dione;

6 $\alpha$ -fluoro-16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ ,21-dihydroxypregna-4-ene-3,20-dione;

5 9 $\alpha$ -fluoro-16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ ,21-dihydroxypregna-4-ene-3,20-dione;

21-acetoxy-16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ -hydroxypregna-4-ene-3,20-dione;

6 $\alpha$ -fluoro-9 $\alpha$ -chloro-budesonide 21-acetate;

10 6 $\alpha$ ,9 $\alpha$ -difluoro-budesonide 21-acetate.

According to the invention, the 16,17-acetonides are reacted with aldehydes having formula  $R_1CHO$ , in molar ratios ranging from 1:1 to 1:5, preferably from 1:1 to 1:1.1, in aqueous hydrofluoric acid and 15 concentrations ranging from 20 to 90%, preferably from 50 to 70%, at a temperature from -70 to 20°C, the temperature being chosen in order to give the desired epimer ratio.

The product is isolated by simple water dilution, in high purity. 20

Although working with unitary stoichiometric ratios between the steroidal substrate and the carbonyl compound, the reaction takes place in almost quantitative yields.

25 Alternatively, instead of hydrofluoric acid, it is possible to use hydrochloric acid. In this case, however, the reaction is less selective in the isomers ratio and the product obtained is less pure.

It should be noted that, in the process of the 30 invention, the acetonide can be replaced by the cor-

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responding diol derivative. Under these conditions the acetal is always produced with an excess of the B epimer, but with a lower selectivity.

Another aspect of the invention, equally important, concerns the conversion of the less active epimer of a 16,17-acetal into the more active epimer. For instance, a mixture of budesonide containing only 30% of the B epimer, subjected to the above mentioned conditions for the preparation of budesonide from the corresponding acetonide, is transformed into budesonide having more than 90% of B epimer. This process is very useful to recover active product from the mother liquors (as deriving from the crystallization) enriched in A epimer. For the epimerization of budesonide like compounds it is sufficient the treatment with hydrofluoric acid alone but, usually, an amount (lower than the stoichiometric one) of the aldehyde (in the instance of budesonide, butyraldehyde) is added in order to avoid any formation of the 16,17-diol.

The following non limiting examples further illustrate the invention. The designation "A epimer" or "B epimer" is made according to US patent No. 3,928,326 and the epimer ratio was determined by HPLC using a reversed phase RP-18 column, eluting with 40% acetonitrile.

#### EXAMPLE 1

50 Grams of desonide (16 $\alpha$ -hydroxyprednisolone-16,17-acetonide) and immediately thereafter 12,5 30 ml of butyraldehyde were added to 500 ml of a 70%

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hydrofluoric acid solution, at -5°C. The mixture was stirred at 0°C for one hour and then poured into 5 liters of demineralized water at 0°C. The precipitate was filtered, washed to neutrality with water and 5 dried under vacuum to give 51 g of pure budesonide with an A/B epimer ratio of 9/91.

#### EXAMPLE 2

The procedure described in Example 1 was repeated, except that the desonide was replaced by other 10 acetonides. The corresponding acetals with butyraldehyde were obtained in almost quantitative yields and with the epimer ratios reported in the following Table.



TABLE

Compound	Starting product	Final product	Ratio A/B epimer
2a	Desonide 21-acetate	Budesonide 21-acetate	13/87
2b	Triamcinolone acetonide	9 $\alpha$ -Fluoro-budesonide	15/85
2c	Fluocinolone acetonide	6 $\alpha$ ,9 $\alpha$ -Difluoro-budesonide	11/89
2d	Flunisolide	6 $\alpha$ -Fluoro-budesonide (6 $\alpha$ -Fluoro-16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ ,21-dihydroxypregna-1,4-diene-3,20-dione)	(Apparently only one epimer)
2e	Flurandrenolide	6 $\alpha$ -Fluoro-16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ ,21-dihydroxypregna-4-ene-3,20-dione	(Apparently only one epimer)
2f	Alcinonide	9 $\alpha$ -Fluoro-21-chloro-16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ -hydroxypregna-4-ene-3,20-dione	12/88
2g	9 $\alpha$ -Fluoro-16 $\alpha$ ,17 $\alpha$ -isopropylidenedioxy-11 $\beta$ ,21-dihydroxypregna-4-ene-3,20-dione	9 $\alpha$ -Fluoro-16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ ,21-dihydroxypregna-4-ene-3,20-dione	9/91
2h	21-Acetoxypregna-16 $\alpha$ ,17 $\alpha$ -isopropylidenedioxy-11 $\beta$ -hydroxypregna-4-ene-3,20-dione	21-Acetoxypregna-16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ -hydroxypregna-4-ene-3,20-dione	10/90
2i	6 $\alpha$ -Fluoro-9 $\alpha$ -chlorodesonide 21-acetate	6 $\alpha$ -Fluoro-9 $\alpha$ -chloro-budesonide 21-acetate	10/90
2j	Fluocinonide	6 $\alpha$ ,9 $\alpha$ -Difluoro-budesonide 21-acetate	ca.15/85

EXAMPLE 3

The procedure described in Example 1, was repeated, except that the reaction was carried out at -78° (and quenching the reaction after 12 hours at this temperature). Budesonide was obtained (A/B ratio 47/53) together with unreacted desonide (about 40%).

EXAMPLE 4

The procedure described in Example 1 was repeated, substituting butyraldehyde by isobutyraldehyde. 16 $\alpha$ -Hydroxyprednisolone 16,17-acetal, apparently only one epimer, was obtained.

EXAMPLE 5

Under the same conditions as in Example 1, but using 16 $\alpha$ -hydroxyprogesterone instead of desonide, budesonide was obtained (A/B ratio 16/84).

EXAMPLE 6

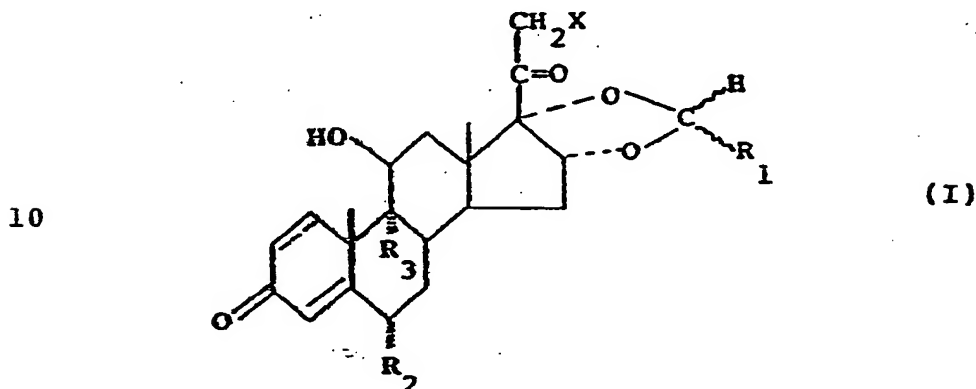
Under the same conditions as in Example 1, but using budesonide (A/B ratio 70/50) instead of desonide, budesonide having A/B ratio of 10/90 was obtained.

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CLAIMS for the Contracting States:

BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A process for the preparation of 16,17-acetals  
5 of pregnane derivatives having formula I



wherein  $R_1$  represents a  $C_1$ - $C_{12}$  alkyl group,  
15 X may be OH, Cl, F or -OCOR group wherein R represents a  $C_1$ - $C_{12}$  alkyl group;

$R_2$  may be hydrogen, fluorine or methyl;

$R_3$  may be hydrogen, fluorine or chlorine;

characterized in that the corresponding 16,17-aceto-  
20 nides are reacted with aldehydes having formula  $R_1\text{CHO}$ , wherein  $R_1$  has the same meaning as in formula I, in aqueous hydrofluoric or hydrochloric acid.

2. The process according to claim 1 characterized  
in that the molar ratio between steroidal acetonide  
25 and aldehyde ranges from 1:1 to 1:5.

3. The process according to claim 2 characterized  
in that the molar ratio between steroidal acetonide  
and aldehyde ranges from 1:1 to 1:1.1.

4. The process according to claims 1-3 characteri-  
30 zed by carrying out the reaction in aqueous hydro-

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fluoric acid and in concentrations ranging from 20 to 90%.

5. The process according to claim 4 characterized by carrying out the reaction in aqueous hydrofluoric acid, in concentrations ranging from 50 to 70% and at temperatures from -10° to 0°C.

6. A process for the preparation of the B epimer of 16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ ,21-dihydroxypregna-1,4-diene-3,20-dione (budesonide) characterized by reacting equimolar amounts of butyraldehyde and 16 $\alpha$ ,17 $\alpha$ -isopropylidenedioxy-11 $\beta$ ,21-dihydroxypregna-1,4-diene-3,20-dione (desonide).

7. The process according to claim 6 characterized by carrying out the reaction in aqueous hydrofluoric acid.

8. The process according to claim 6 characterized by carrying out the reaction in aqueous hydrochloric acid.

9. Process for the preparation of the B isomer of pregnane acetal derivatives having formula I characterized in that the corresponding A epimer is reacted with aqueous hydrofluoric acid.

10. The process according to claim 9 characterized by carrying out the reaction in the presence of the corresponding aldehyde with molar ratios ranging from 0.1 to 1.0 moles/mole of acetal.

11. The process according to claims 9 or 10 for the preparation of the B epimer of budesonide starting from the corresponding A epimer.

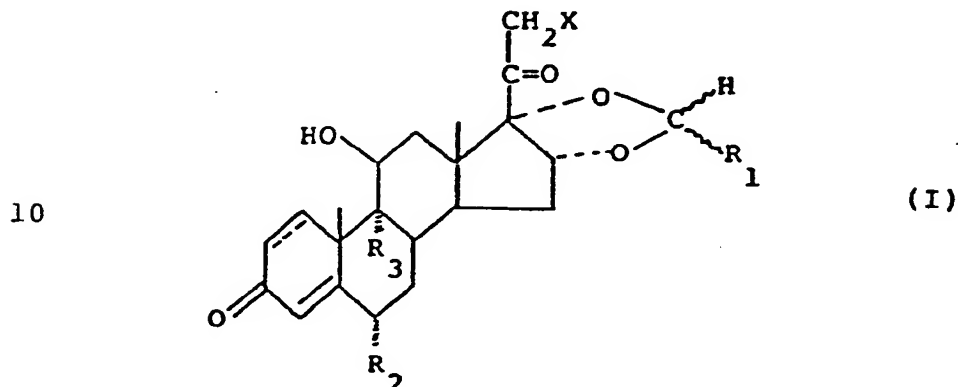
12. A process for the preparation of pregnane ace-

tal derivatives of formula I characterized in that the corresponding 16,17-diols are reacted with aldehydes of formula  $R_1HCO$  in aqueous hydrofluoric or hydrochloric acid.

- 5 13. As a new compound, 6 $\alpha$ -fluoro-16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ ,21-dihydroxypregna-1,4-diene-3,20-dione.
14. As a new compound, 9 $\alpha$ -fluoro-21-chloro-16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ -hydroxypregna-4-ene-3,20-dione.
- 10 15. As a new compound, 6 $\alpha$ -fluoro-16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ ,21-dihydroxypregna-4-ene-3,20-dione.
16. As a new compound, 9 $\alpha$ -fluoro-16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ ,21-dihydroxypregna-4-ene-3,20-dione.
17. As a new compound, 21-acetoxy-16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ -hydroxypregna-4-ene-3,20-dione.
- 15 18. As a new compound, 6 $\alpha$ -fluoro-9 $\alpha$ -chloro-budesonide 21-acetate.
19. As a new compound, 6 $\alpha$ ,9 $\alpha$ -difluoro-budesonide 21-acetate.

CLAIMS for AT

1. A process for the preparation of 16,17-acetals  
5 of pregnane derivatives having formula I



- wherein  $R_1$  represents a  $C_1$ - $C_{12}$  alkyl group,  
15 X may be OH, Cl, F or -OCOR group wherein R represents a  $C_1$ - $C_{12}$  alkyl group;  
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characterized in that the corresponding 16,17-aceto-  
20 nides are reacted with aldehydes having formula  $R_1CHO$ , wherein  $R_1$  has the same meaning as in formula I, in aqueous hydrofluoric or hydrochloric acid.
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25 and aldehyde ranges from 1:1 to 1:5.
3. The process according to claim 2 characterized in that the molar ratio between steroidal acetonide and aldehyde ranges from 1:1 to 1:1.1.
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fluoric acid and in concentrations ranging from 20 to 90%.

5. The process according to claim 4 characterized by carrying out the reaction in aqueous hydrofluoric acid, in concentrations ranging from 50 to 70% and at temperatures from -10° to 0°C.

6. A process for the preparation of the B epimer of 16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-11 $\beta$ ,21-dihydroxypregna-1,4-diene-3,20-dione (budesonide) characterized by reacting equimolar amounts of butyraldehyde and 16 $\alpha$ ,17 $\alpha$ -isopropylidenedioxy-11 $\beta$ ,21-dihydroxypregna-1,4-diene-3,20-dione (desonide).

7. The process according to claim 6 characterized by carrying out the reaction in aqueous hydrofluoric acid.

8. The process according to claim 6 characterized by carrying out the reaction in aqueous hydrochloric acid.

9. Process for the preparation of the B isomer of pregnane acetal derivatives having formula I characterized in that the corresponding A epimer is reacted with aqueous hydrofluoric acid.

10. The process according to claim 9 characterized by carrying out the reaction in the presence of the corresponding aldehyde with molar ratios ranging from 0.1 to 1.0 moles/mole of acetal.

11. The process according to claims 9 or 10 for the preparation of the B epimer of budesonide starting from the corresponding A epimer.

12. A process for the preparation of pregnane ace-

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tal derivatives of formula I characterized in that the corresponding 16,17-diols are reacted with aldehydes of formula  $R_1HCO$  in aqueous hydrofluoric or hydrochloric acid.





Europäisches Patentamt  
European Patent Office  
Office européen des brevets

(19)

(11) Publication number:

**0 164 636**  
**A3**

(17)

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(51) Int. Cl.<sup>4</sup>: C 07 J 71/00

(22) Date of filing: 28.05.85

(30) Priority: 11.06.84 IT 2134384

(43) Date of publication of application:  
18.12.85 Bulletin 85/51

(68) Date of deferred publication of search report: 08.10.86

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EP 0 164 636 A3



European Patent  
Office

# EUROPEAN SEARCH REPORT

0164636

Application number

EP 85 10 6522

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X,D	EP-A-2 185 405 (A.B. BOFORS) * Claims 1,4,5,10 * ---	1,19	C 07 J 71/00
A	EP-A-0 054 010 (AB DRACO) * Claims * ---	1	
A,D	US-A-3 928 326 (RALPH LENNART BRATTSAND) * Claims * -----	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 J 71/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 09-07-1986	Examiner HENRY J.C.
<b>CATEGORY OF CITED DOCUMENTS</b>			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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